

PHYSIOLOGICAL ACTION OF SULPHONAL.

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(From the private Laboratory of Dr. Ott.)

SULPHONAL was discovered by Prof. Baumann in 1886, and its chemical formula is $(\text{CH}_3)_2\text{C}=(\text{SO}_2\text{C}_2\text{H}_5)_2$ (diethyl-sulphon-dimethyl-methane). It is a white crystalline powder, melts at 125.5° , and is soluble in from 18 to 20 parts of boiling water, recrystallizes on cooling, and is practically insoluble in water at the ordinary temperature, 450 parts, according to Kast, being necessary to dissolve it. Its solubility is much increased, however, by the addition of salts, hydrochloric acid, and peptones.

It is odorless and tasteless, except to the most sensitive, to whom it possesses a slightly bitter, unpleasant taste.

It was first clinically introduced by Prof. A. Kast,¹ of Freiburg, who speaks of it in the highest terms as an hypnotic. He says of it, "Sulphonal deserves a prominent position among medical agents, not only as an hypnotic for producing temporary insensibility, but for its property of assisting the normal periodical want of sleep. It produces no harmful effects on the elements of the blood, it does not attack and impair the stomach, and even in large doses it calls forth no dangerous derangement of the function of the heart or the vascular system." He found it especially useful in cases of nervous insomnia, where many of the more powerful or "drastic" hypnotics do much harm.

Since Kast's observations, many clinicians have given the drug a thorough trial, and their opinions in the main coincide with his. Dr. G. Rabbas² says: "Sulphonal in moderate doses of two to three grammes acts more safely and effectively than either amylehydrate or paraldehyde in even

¹ Berliner Klinische Wochenschrift, 1888.

² Berlinischer Klinische Wochenschrift, 1888, No. 17.

larger doses. Where patients are accustomed to the use of narcotics, sulphonal is even more successful." Moreover, he claims that the action is more prolonged than that of chloral, but not as prompt, sleep ensuing from one-half to two hours after the administration of the drug, lasting from six to eight hours. The sleep is normal and unbroken, leaving the patient very much benefited. He concludes by saying, "The results of my investigations induce me to give unqualified approval of sulphonal."

Dr. H. Rosin³ employed sulphonal in 274 separate cases, and says that he has found sulphonal, in doses of two grammes, is equally efficacious as morphia and chloral, and on account of its harmlessness he recommends it very highly. Dr. Carl Oestreicher has used it in over 100 cases, and speaks very highly of it. Dr. Julius Schwalbe reports its use in over 50 cases, and finds vertigo and headache as after-effects in a slight percentage of his cases. The ordinary dose of the drug is about thirty grains; and fifteen grain doses, according to Kast, are large enough for women. Forty-five grains have been given without unpleasant effect, though a drachm produced a deep sleep, lasting from eight to twelve hours, followed by a staggering feeling on the following day.

Rosin found thirty grains equal to one-sixth to one-quarter grains of morphia. Rabbas claims that doses of four grammes, alternated at short intervals with doses of two to three grammes, are harmless. Schmey⁴ found that two grammes in a case of angina pectoris produced no sleep, but aggravated the condition of the patient.

These observations induced me to study more carefully the physiological action of this drug. The article I used was sulphonal "Riedel." It was dissolved by the aid of warm water, and injected subcutaneously or by the jugular. The experiments were made upon frogs and rabbits.

GENERAL ACTION.

EXP. I.—A small frog received subcutaneously, at 3 P. M., 1.04 grains of sulphonal.

³ Berliner Klinische Wochenschrift, No. 25.

⁴ Centralblatt f. Medicinischen Wissenschaften, 1888, No. 46.

- 3.20 P.M.—Is very quiet.
 3.25 “ All voluntary activity is abolished; reflexes unchanged.
 4.35 “ In same condition as at 3.25 P.M. Next day was quite well.

EXP. II.—A large rabbit received at 3.25 P.M. Six grains of sulphonal in capsule, which was pushed down the œsophagus. At 5.00 P.M. no effect was observed, probably on account of its insolubility. The next day the animal was weak, staggered, and was inclined to be very quiet.

EXP. III.—Large rabbit.

- 2.40 P.M.—Received subcutaneous injections of 3 grains of sulphonal.
 2.45 “ Pupil slightly contracted, and moves about.
 3.15 “ 3 grains of sulphonal injected.
 3.30 “ 9 grains of sulphonal injected.
 3.35 “ Animal very quiet; when he attempts to move, staggers.
 4.15 “ Animal asleep.
 5.00 “ Animal deeply narcotised.

A cut was made in the ear, from which some blood was obtained; this was placed in the field of a Sorby-Browning spectroscope, but only the normal bands of oxyhæmoglobin were seen.

EXP. IV.—Rabbit. Normal pupil, $9\frac{1}{2}$ millimetres.

- 2.00 P.M.—Subcutaneous injection of 4 grains of sulphonal.
 2.55 “ 4 grains of sulphonal injected; no change in the pupil.
 3.00 “ Pupil 9 millimetres in diameter. Animal is very quiet; when made to move, staggers. When placed upon its side, does not attempt to right itself.
 3.30 “ 18 grains of sulphonal injected subcutaneously. Pupil 8 millimetres in diameter.
 4.00 “ Animal asleep.
 Next day the animal is in a dazed and staggering condition.

These experiments prove that sulphonal by the stomach acts very slowly on account of its insolubility, that the sub-

cutaneous warm solution of sulphonal is much more active.

They also show that it is a narcotic, followed by a state of general relaxation of the muscles of the body and a staggering gait next day.

The oxygenation of the blood does not seem to be affected, using spectroscopic tests. The pupil is slightly contracted. Whether directly or indirectly due to the drug, I am not prepared to state.

MOTOR NERVES.

EXP. V.—Frog, unusually large, strong and active.

2.40 P.M.—Injected subcutaneously, 7 grains of sulphonal.

3.00 “ No loss of sensibility, quiet, weak in anterior extremities; when pinched, tried to hop, but was unable.

3.07 “ Injected .4 grains of sulphonal; struggles, lies flat on its back when placed in that position.

3.32 “ Injected .345 grains of sulphonal; sensibility diminished.

3.41 “ Animal is quiet, flattened out, no movement whatever, pupil slightly contracted.

4.00 “ Is lying on back, relaxed, unable to move; loss of all voluntary motion. Sciatic nerve irritable at 440 millimetres, Du Bois inductorium.

Several days later was in normal condition.

This experiment demonstrated that the motor nerves were quite irritable in deep narcosis.

MUSCULAR ACTION.

EXP. VI.—Frog received subcutaneously .6 grains of sulphonal; brain and spinal cord destroyed. The gastrocnemius was attached to Marey's myograph and loaded with a weight of ten grammes; single induction shocks were sent through the muscles, and the curves registered on the smoked drum of a Marey-Foucault regulator. The time of the contractions was noted by a tuning-fork registering 240 vibrations per second. Several experiments showed no change from that seen normally.

This led us to infer that the loss of sensibility is not due to lesions of the muscles.

SENSORY NERVES.

EXP. VII.—A small and lively frog had the blood-vessels of the right leg ligatured; .6 grains of sulphonal were injected. After a short time, the reflex action of each posterior extremity was tested by a watery solution acidulated with sulphuric acid. The time it took each extremity to be withdrawn was noted by the metronome making 100 beats per minute.

P.M.	LEFT LEG.	RIGHT LEG.
2.40	9	8
2.45	10	9
2.50	10	9
3.00	9	9
3.06	9	9
3.10	8	7
3.15	8	9
3.24	13	16
3.27	16	14
3.35	11	11

EXP. VIII.—Frog in the same condition as the preceding one; blood-vessels of the right leg ligatured at 3.40 P.M. Sulphonal given subcutaneously.

P.M.	LEFT LEG.	RIGHT LEG.
3.45	15	15
3.48	12	10
4.00	8	8
4.12	11	8
4.15	8	8
4.22	9	9
4.27	9	10
4.35	8	9

It is evident from the preceding experiments that as the loss of sensibility is equal in the leg in which the poison is excluded, the cause is not in the peripheral terminations of the sensory nerves. It has already been shown not to be in the muscles or motor nerves, hence it must be in the central nervous system.

REFLEX ACTION.

EXP. IX.—Frog. Cerebrum ablated. Reflex action tested by a metronome beating 100 per minute; irritant used, water slightly acidulated with sulphuric acid.

TIME.	METRONOME BEATS.
2.45 P.M.	27
3.12 "	20
3.15 " Injected .2 grains of sulphonol.	
3.16 "	31
3.20 "	49
3.35 "	33
3.43 "	58

EXP. X.—Conditions same as Exp. IX.

TIME.	METRONOME BEATS.
3.00 P.M.	20
3.08 " Injected .3 grains of sulphonol.	
3.24 "	25
3.27 "	39
3.40 "	55
3.45 "	44
3.49 "	34
3.56 "	38

EXP. XI.—Frog. Conditions same as in Exp. X.

TIME.	METRONOME BEATS.
2.30 P.M.	20
2.35 "	19
2.36 " Injected .6 grains of sulphonol.	
2.40 "	32
2.45 "	28
2.50 "	32
2.55 "	27
3.00 "	26
3.05 "	23
3.10 "	23
3.15 "	21

EXP. XII.—Frog. Conditions same as Exp. XI.

TIME.	METRONOME BEATS.
2.30 P.M.	15
2.35 "	14
2.37 " Injected .3 grains of sulphonol.	
2.45 "	10
2.55 "	4
3.00 "	4
3.05 "	4
3.10 "	3
3.15 "	3
3.35 "	3

EXP. XIII.—Conditions same as Exp. XII.

TIME.	METRONOME BEATS.
2.40 P.M.	20
2.43 "	20
2.45 " Injected .6 grains of sulphonal.	
2.55 "	38
3.00 "	40
3.05 "	46
3.10 " Cut off the medulla.	
3.15 "	20
3.20 "	15
3.25 "	16
3.30 "	23
3.40 "	30
3.45 "	32

EXP. XIV.—Conditions same as Exp. XIII.

TIME.	METRONOME BEATS.
3.00 P.M.	28
3.05 "	26
3.11 " Injected .6 grains of sulphonal.	
3.15 "	25
3.20 "	28
3.25 "	30
3.35 "	27
3.45 "	28
3.50 "	18
3.55 "	29
4.00 " Injected .6 grains of sulphonal.	
4.04 "	42
4.10 "	23
4.13 "	25
4.25 " No response.	

EXP. XV.—Frog. Entire brain severed from the cord; animal unusually lively.

TIME.	METRONOME BEATS.
3.00 P.M.	20
3.05 " Injected .6 grains of sulphonal.	
3.10 "	27
3.15 "	22
3.18 "	21
3.21 "	22
3.24 "	15
3.29 "	15
3.35 "	17
3.40 "	22
3.47 "	22

EXP. XVI.—Frog. Conditions same as Exp. XV.

TIME.	METRONOME BEATS.
2.45 P.M.	16
2.50 " Injected .2 grains of sulphon.	
2.55 "	24
3.00 "	13
3.03 "	13
3.06 "	15
3.11 "	19

EXP. XVII.—Frog. Conditions same as Exp. XVI.

TIME.	METRONOME BEATS.
3.49 P.M.	13
3.57 " Injected .6 grains of sulphon.	
4.01 "	12
4.06 "	12
4.11 "	10
4.16 "	15
4.20 "	12
4.25 "	14

EXP. XVIII.—Frog. Conditions same as Exp. XVII.

TIME.	METRONOME BEATS.
4.50 P.M.	16
4.52 " Injected .2 grains of sulphon.	
4.56 "	14
5.00 "	16
5.05 "	24
5.10 "	25
5.15 "	21
5.18 "	22
5.25 "	21

Usually it reduces reflex action, occasionally it increases it.

When Setschenow's inhibitory centres are removed, sulphon. does not diminish the reflex activity. The inference would be that it stimulates Setschenow's centres, thus decreasing reflex activity.

CIRCULATION.

EXP. XIX.—Frog. Brain destroyed, heart exposed.

TIME.	HEARTBEATS PER MINUTE.	REMARKS.
2.45 P.M.	22	
2.50 "		Injected .8 grains of sulphonol.
2.55 "	28	
3.00 "	25	
3.05 "	25	
3.10 "	24	
3.15 "	22	
3.20 "	22	
3.25 "	21	
3.30 "	20	
3.45 "	19	
4.00 "	19	

EXP. XX.—Rabbit, etherized; carotid and jugular prepared, Ludwig's Kymographion attached.

TIME.	PULSE.	PRESSURE.	REMARKS.
3.40 P.M.	42	72	
3.40.15 "	46	76	Injected 2½ grs. sulphonol.
3.40.30 "	40	40	
3.41 "	41	64	
3.42 "	44	68	
3.44 "	44	76	
3.45 "	46	72	
4.00 "	46	88	
4.01.15 "	48	90	
4.01.30 "	45	68	Injected .5 grs. sulphonol.
4.01.45 "	46	48	
4.02 "	46	44	
4.03 "	44	74	
4.04.15 "	46	88	
4.21 "	44	110	
4.22 "	46	108	
4.23.15 "	44	100	
4.24.15 "	49	98	
4.24.45 "	46	102	

EXP. XXI.—Conditions same as Exp. XX.

TIME.	PULSE.	PRESSURE.	REMARKS.
3.32.15 P.M.	53	94	
3.32.30 "	55	86	Injected 3.7 grs. sulphonol.
3.32.85 "	59	82	
3.33 "	59	84	
3.34 "	59	98	
3.35 "	59	96	
3.51 "	58	116	
3.52.30 "	63	122	
3.54.30 "	62	122	

EXP. XXII.—Rabbit. Conditions same as in Exp. XXI.

TIME.	PULSE.	PRESSURE.	REMARKS.
2.37.45 P.M.	63	116	Injected 2 grs. of sulphonol.
2.38 "	63	118	
2.38.15 "	63	94	
2.38.30 "	63	94	
2.39 "	63	110	
2.41 "	62	122	Injected 3.7 grs. sulphonol.
2.47 "	59	120	
2.47.30 "	61	118	
2.47.45 "	61	118	
2.48 "	62	110	
2.48.15 "	64	106	
2.49 "	60	114	
2.50 "	58	122	Injected 5.5 grs. sulphonol.
2.53 "	—	124	
3.04 "	—	116	
3.04.15 "	—	104	
3.04.30 "	—	64	
3.05 "	—	—	Animal killed.

These experiments demonstrate that upon the heart sulphonol has but little activity, usually slightly increasing its rapidity. As to arterial tension, immediately after the injection by the jugular it is decreased; afterward, however, it is increased considerably; the opposite case happens with chloral.

RESPIRATION.

EXP. XXIII.—Rabbit. Tracheal canula attached to Marey's polygraph; jugular prepared.

TIME.	RESPIRATIONS.	REMARKS.
2.45 P.M.	31	Injected .2 grains of sulphonol.
2.45.15 "	29	
2.45.30 "	29	
2.45.45 "	29	
2.46 "	30	
2.46.15 "	25	
2.47 "	17	
2.48 "	16	
2.48.15 "	14	
2.48.30 "	13	
2.50 "	12	
2.51 "	11	
2.53 "	8	Animal killed.

EXP. XXIV.—Conditions same as Exp. XXIII.

TIME.	RESPIRATIONS.	REMARKS.
3.35 P.M.	14	
3.35.30 "	20	
3.36 "	20	Injected .1 grains of sulphonol.
3.36.15 "	21	
3.36.30 "	15	
3.37 "	13	
3.37.30 "	11	Pulse, 254.
3.45 "	10	
3.48.30 "	15	
3.48.45 "	13	Injected .1 grains of sulphonol.
3.49 "	16	
3.51.15 "	10	Pulse, 280.
3.58 "	12	
4.05 "	13	
4.05.30 "	15	Injected .2 grains of sulphonol.
4.05.45 "	11	
4.06.15 "	12	
4.06.30 "	12	Injected .2 grains of sulphonol.
4.07 "	13	
4.08.45 "	12	
4.09.45 "	14	
4.10 "	15	
4.11 "	14	
4.13 "	14	

Animal taken off, lively, no staggering.

EXP. XXV.—Rabbit. Vagi cut.

TIME.	RESPIRATIONS.	REMARKS.
4.30 P.M.	7	
4.30.15 "	8	
4.31 "	9	Injected .1 grains of sulphonol.
4.31.15 "	9	
4.31.30 "	10	
4.32.15 "	11	
4.32.30 "	12	
4.33 "	13	
4.34 "	12	
4.36 "	13	
4.37 "	12	
4.40 "	11	
4.46.45 "	12	
4.47 "	10	Injected .2 grains of sulphonol.
4.47.15 "	11	
4.47.30 "	8	
4.48 "	8	

TIME.		RESPIRATIONS.	REMARKS.
4.49	P.M.	8	
5.50	"	9	
4.50.30	"	10	
5.51.45	"	9	
5.00	"	9	
5.04	"	9	
5.05	"	8	
5.08	"	5	
5.09.15	"	7	
5.10	"	9	
5.11.15	"	9	

The preceding experiments prove that sulphonal decreases the rapidity of the respirations.

Section of the vagi does not alter the result.

My conclusions as to sulphonal are as follows:

- (1) It does not affect the irritability of the motor nerves.
- (2) It does not alter the muscle curve.
- (3) The sensory nerves are left intact.
- (4) It depresses reflex activity mainly by an action on Setschenow's centres, occasionally it exalts reflex excitability.
- (5) It acts as a narcotic.
- (6) The pulse is usually somewhat accelerated.
- (7) The arterial tension, after a temporary fall, is considerably increased.
- (8) Respiration is depressed, section of the vagi does not alter the effect.

These facts lead me to believe that sulphonal will replace chloral to a considerable extent. The well known dangerous action of chloral as to heart and respiration is avoided with this drug, and if the narcotic effects are equal sulphonal should have the preference. Whilst I have seen the heart paralyzed by the drug in a few minutes, yet it was due to the sudden action of the drug by the jugular and perhaps partly to some of the drug being thrown down on account of its insolubility, for the solution was somewhat warmer than the temperature of the blood.